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EXAMINER
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1634	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/778,900	SMITH, JOHN C.	
	Examiner	Art Unit	
	Juliet C Einsmann	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *8-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-7 and 19, particularly with regard to the SNP at position 3888 according to the position defined by EMBL Accession No. X51602 in Paper No. 12 is acknowledged. Applicants point out that claim 1 covers a method of diagnosis involving determining the sequence at "one or more" of the nine specified positions and that if the restriction requirement is allowed to stand it will limit applicants to claiming methods for determining the sequence at only one of the positions. This is not persuasive, nor is it necessarily accurate. Claims which particularly require the examination of more than one polymorphic site were not present when the restriction requirement was set forth. The claims, as presented and restricted, only **required** the determination of the sequence at a single polymorphic site. The current claim set includes claim 20 which requires the determination of the sequence present for all nine listed polymorphic sites. This claim is not separated from the elected polymorphism, but this does not remove the fact that claims which require only one of the polymorphisms are still restricted one from another. The restriction requirement was based on the claim set as presented, not a hypothetical claim set. Thus, since the claims requires only the sequencing of a single position, and all nine of the recited positions are independent and distinct from one another and the search and examination of all nine separately would pose a significant burden to the examiner, the requirement that applicant select a single polymorphism for examination is proper and maintained. Claim 20 will be examined within the elected invention because it is within the scope of the elected invention.

The requirement is therefore made FINAL.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Detection of Polymorphisms in the Human FLT-1 Gene.

3. The disclosure is objected to because of the following informalities: The specification and claims repeatedly refer to EMBL accession numbers instead of reciting sequences or sequence identifiers. This recitation is similar to the recitation of a trademark, in that the EMBL accession number does not represent a fixed disclosure of a sequence, but instead refers to a record that is constantly able to be updated and modified. Applicant should amend the specification to include the sequences which are referred to by EMBL accession numbers (and comply with the remainder of the sequence rules) and file a 132 declaration with evidence showing and stating that the newly filed sequence is identical to the sequence that was in EMBL at the time the invention was filed.

Claim Objections

4. Claims 4 and 6 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. Both claims 4 and 6 are multiply dependent and depend from at least 3 which is also multiply dependent. See MPEP § 608.01(n). Accordingly, the claims 4 and 6 not been further treated on the merits. However, it is noted that claims 4 and 6 are rejected herein insofar as they depend from rejected claims and thus encompass all of the limitations of the claims from which they depend. With regard to 112 2nd and the prior art, however, these claims have not been specifically addressed.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 2, 3, 4, 5, 7, 19, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite over the recitation "determining the sequence of the nucleic acid of the human at one or more of positions..." because it is unclear how you determine a sequence at a single position of a nucleic acid. The word "sequence" implies the determination of the nucleotide present at more than one position of a nucleic acid, yet the claim sets forth that the sequence is determined at one or more of the recited positions. It is not clear how a sequence can be determined at a particular position. Amendment of the claim to recite, for example, "determination of the nucleotide present at position 3888 of SEQ ID NO: 1" would obviate this rejection. All of the claims that depend from claim 1 are rejected because they incorporate this limitation but do not clarify the problem.

Claims 1, 2, 3, 4, 5, 7, 19 and 20 are indefinite over the recitation of EMBL accession numbers (X51602 and D64016) because it is not clear as to what is encompassed by these recitations. The sequences listed in the EMBL database are continuously updated and modified. Therefore, there is no single, fixed definition for the sequences presented as EMBL Accession No. X51602 and D64016.

Claim 1 is further indefinite over the recitation "determining the status of the human by reference to polymorphism" because it is not clear what this step is requiring. It is not clear what

it means to determine the status of a human "by reference to polymorphism." Claim 7 is indefinite because it recites the same language.

Claim 7 is indefinite for failing to recite a final process step which agrees back with the preamble. Claim 7 is drawn to a method for the diagnosis of flt-1 ligand mediated disease, yet the claim recites a final step of determining the status of the individual by reference to polymorphism in the flt-1 gene. The claim does not set forth the relationship between the determining the status of the individual by reference of the to polymorphism and the diagnosis of disease and therefore, it is not clear whether the claim is intended to be drawn to a method for diagnosis of disease or a determining the status of polymorphism. It is not clear if determining the status of the individual accomplishes the diagnosis or if some additional steps are required.

Claim 19 is indefinite because the phrase "the flt-1 gene sequence" in lines 2-3 of the claim does not have proper antecedent basis in the claim. The claim does not previously refer to a flt-1 gene sequence, thus it is not clear which one is "the flt-1 gene sequence."

Claim 19 is indefinite because the phrase "the polymorphism" in line 3 of the claim does not have proper antecedent basis in the claim. The claim does not previously refer to polymorphisms.

Claim 19 is indefinite over the recitation "which sequence includes at least one of the polymorphisms at position:..." because it is unclear if the claim is requiring that the nucleic acid of at least 20 consecutive nucleic acids form the flt-1 gene overlap with position 3888 of EMBL accession number X51602 or if it merely must contain the nucleotide that is located at the recited position(s). The polymorphism taught in the specification for position 3888 of EMBL accession number X51602 is a single nucleotide base change at a single position. For example, in EMBL

X51602, there is a "C" at position 3888. Thus, is the claim requiring that the 20 consecutive nucleic acids must also contain a "C," or does applicant intend for the claim to require that the nucleic acid sequence comprising at least 20 consecutive bases overlap with and contain position 3888 of EMBL accession number X51602 as well as sequence from within the EMBL sequence that is contiguous to position 3888, or some other interpretation? Clarification is required.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 4-7 rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

It is noted that the instant claims each recite methods which comprise the detection of nucleotide sequences at one or more of nine different polymorphic sites. A restriction requirement was set forth in which applicant was required to select a single polymorphic site for examination. Applicant selected the polymorphism at position 3888 of EMBL accession number X51602. This utility rejection considers only this site in the claims.

The instant claims are drawn to methods for the diagnosis of a polymorphism in a human FLT-1 gene, methods for assessing and individual for a predisposition and/or susceptibility of an individual to FLT-1mediated disease, and methods for diagnosis of FLT-1mediated disease. Each of the methods comprise steps in which the particular nucleotide present is detected at a particular position in EMBL accession number X51602.

The specification teaches that the FLT-1 gene has been associated with a number of diseases and physiological states, including angiogenic diseases and cancers (p. 1). Further, the specification provides nine polymorphisms in the FLT-1 gene. In particular, the specification teaches a polymorphic site at position 3888 of EMBL accession number X51602, which is within the coding sequence of the FLT-1 gene. This polymorphism does not cause a change in the encoded polypeptide sequence. The specification teaches that "polymorphisms which do not result in amino acid changes (silent polymorphisms) or which do not alter any known consensus sequences may nevertheless have a biological effect, for example, altering mRNA folding, stability, splicing, transcription rate, translation rate, or fidelity (specification, page 3, lines 20-23)." The specification also teaches that methods for detection of polymorphisms can be used to identify patients most suited to therapy with particular pharmaceutical agents. Furthermore, the specification and claims suggest that the methods can be used to detect a FLT-1 mediated disease.

None of these asserted utilities meet the standard of being specific, substantial, and credible. Generally, these are utilities that can be assigned to a broad class of invention, that is any method for detecting a polymorphism, thus they are not specific. Furthermore, the utilities set forth are not considered to be substantial because further experimentation would be required to reasonably confirm that the disclosed polymorphism is in fact diagnostic or prognostic of disease or in fact associated with the suitability of a particular pharmaceutical agent. The specification merely postulates that such utilities exist, but in order to practice the claimed invention, further experimentation would be required to determine an association between the polymorphism and some physiological state or disease.

Claims 4-7 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The utility rejection has not been applied to claims 1-3 and 19-20 because these claims encompass an embodiment that would have utility, namely the sequencing of the FLT-1gene, which itself is known to be associated with physiological and disease states (see specification, page 1). If the claims are narrowed to exclude this embodiment, these claims may be included in the utility rejection.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-7 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting and sequencing the human flt-1 gene and portions thereof, does not reasonably provide enablement for methods which are limited to the detection of a polymorphism at position 3888 of EMBL accession number X51602 or for methods of diagnosis or prognosis of a disease via the detection of a polymorphism at position 3888 of EMBL accession number X51602. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention commensurate in scope with these claims.

This rejection applies to the instant claims insofar as they might be interpreted as methods for the detection of the presence or absence of particular single nucleotide

polymorphisms. Insofar as the instant claims read generally on methods for sequencing the human flt-1 gene, this rejection does not apply (see prior art rejections herein). The teachings of the specification (at, e.g., page 21) and of the prior art as exemplified by Shibuya et al. (1990) disclose methods of detecting and sequencing the FLT-1gene and portions thereof. Such methods are encompassed by the instant claims as written, and a person skilled in the art could clearly practice methods of detecting and sequencing a known gene without further guidance. However, it is unpredictable as to whether one of skill in the art could practice without undue experimentation methods requiring detection of the polymorphism at position 3888 of EMBL accession number X51602, which methods are also encompassed by the claims.

It is noted that the instant claims each recite methods which comprise the detection of nucleotide sequences at one or more of nine different polymorphic sites. A restriction requirement was set forth in which applicant was required to select a single polymorphic site for examination. Applicant selected the polymorphism at position 3888 of EMBL accession number X51602. This enablement rejection considers only this site in the claim. With regard to claim 20, many of the examples in this rejection are directed at the elected polymorphism, but it is to be understood that the rejection applies to claim 19 also which requires the examination of nine different polymorphic sites.

The instant claims are drawn to methods for the diagnosis of a polymorphism in an FLT-1 gene in a human, methods for assessing and individual for a predisposition and/or susceptibility of an individual to FLT-1 mediated disease, and methods for diagnosis of FLT-1 mediated disease. Each of the methods comprise steps in which the particular nucleotide present is detected at a particular position in EMBL accession number X51602.

The specification teaches that the FLT-1 gene has been associated with a number of diseases and physiological states (p. 1). Further, the specification provides nine polymorphisms in the FLT-1gene. In particular, the specification teaches a polymorphic site at position 3888 of EMBL accession number X51602, and that this particular polymorphism is a silent polymorphism, resulting in no change in the encoded amino acid sequence. Although the specification teaches that in general, "polymorphisms which do not result in amino acid changes (silent polymorphisms) or which do not alter any known consensus sequences may nevertheless have a biological effect, for example, altering mRNA folding, stability, splicing, transcription rate, translation rate, or fidelity (specification, page 3, lines 20-23)," the specification is silent with respect to the effect of this polymorphism on the functioning of FLT-1 gene. The specification does not disclose any relationship between the presence of this polymorphism and any particular disease state or physiological condition.

The art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. The prior art teaches a polymorphic dinucleotide repeat in the FLT-1 gene. Parry et al. postulated that this polymorphism would be associated with minimal change nephropathy, but were unable to demonstrate any association between this polymorphism and the disease state (Parry et al. European Journal of Immunogenetics, Vol. 26, pages 321-323). Furthermore, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior

studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Finally, in some cases where multiple polymorphisms are identified in a gene, some of these are demonstrated to be disease associated and some are not. Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma but some of these are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined to not have a statistical association with asthma (p=0.294). Thus, even for SNPs within the same gene, it is highly unpredictable as to whether a particular marker will be disease associated.

The level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, but the unpredictability in the art is higher. While the instant specification has disclosed a number of different polymorphisms in the FLT-1 gene, it remains highly unpredictable as to the biological significance of these polymorphisms. Thus, the claimed method directed towards the diagnosis of polymorphisms, or the diagnosis or prognosis of disease via detection of polymorphisms, for enablement of the full scope, requires the knowledge of unpredictable and potentially non-existent associations between the instantly elected polymorphism and some

phenotypic trait. Even if the elected polymorphism is in some way associated with some disease, it is difficult (if not impossible) to know or predict from the teachings of the specification which disease or how the polymorphism is associated. That is, it is unpredictable as to whether the presence of a particular allele the polymorphism would confer a higher or lower likelihood of having the disease. In this case, the possible uses for the claimed methods are undefined, beyond the suggestion that they can be used to detect a disease associated with the FLT-1 gene.

The amount of direction or guidance presented in the specification with regard to how to use the instant invention is minimal. With regard to claims directed towards simple detecting the presence of the gene polymorphism, the specification implies that these methods are useful to determine proper pharmacological treatments or to detect diseases. However, since the effects of any given polymorphism on gene activity are highly unpredictable, it is impossible to predict from the teachings of the instant specification what identifications can be made using the instantly claimed methods. That is, the specification does not provide any guidance as to how the polymorphism at position 3888 of EMBL accession number X51602 would be associated with any pharmaceutical agent. The specification does not discuss whether this particular polymorphism will increase the likelihood of a positive or negative response to any drug. Furthermore, with regard to methods that particularly recite the diagnosis or prognosis of disease, the specification does not provide any guidance, other than the suggestion that these methods could be carried out for "flt-1 ligand mediated diseases." The specification provides no guidance or working examples that teach or demonstrate the ability to use the disclosed polymorphic site as a marker for any disease in particular, or for disease in general.

The quantity of experimentation required to discover how to use the instant invention is very high. In order to use the claimed invention, one would have to establish a relationship between the polymorphism at nucleotide 3888 of EMBL accession number X51602 some physiological or disease state. Indeed, even to use the method of claim 1 to identify patients suited for particular pharmaceutical agents, one would need to know that the polymorphism at nucleotide 3888 of EMBL accession number X51602 was in some way associated with response to some pharmaceutical agent. In order to obtain the type of information necessary to practice the claimed invention, one would be required to undertake the screening of hundreds or thousands of patients as well as possible hundreds of diseases or pharmaceutical agents. Even if such experiments were undertaken, it would still be unpredictable as to whether any associations would be detected, in light of the unpredictability of such associations, as already discussed. Thus, while one could perform further research to determine whether applicant's method would be useful in disease detection and/or treatment, it is unknown as to what the outcome of such research might be and as to whether any quantity of experimentation would result in the identification of an association between the C/T polymorphism at position 3888 and any disease or condition. Further, absent a teaching the C/T polymorphism at position 3888 is not associated with such conditions, it is further unpredictable as to whether detection of the C/T polymorphism at position 3888 would be useful in predicting, e.g., the absence or decreased likelihood of such conditions.

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of direction or working examples in the specification, and the high quantity of experimentation that would be required to practice the claimed invention, it is

concluded that undue experimentation would be required to use the instantly claimed invention. Thus, with respect to claims 1-5 and 19, although the specification certainly enables one to detect the presence of the polymorphism (i.e. the "make" portion of 112 1st paragraph), it would require undue experimentation in order to determine how to use the methods of claims 1-5 and 19. Furthermore, with respect to claims for methods of diagnosis or prognosis, it is concluded that it would require undue experimentation to determine the particular disease state that can be diagnosed and thus to practice the claimed invention commensurate in scope with the present claims.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 2 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Shibuya et al. (Oncogene, 1990 April, 5(4) 519-524).

Shibuya et al. teach a method for the diagnosis of a polymorphism in an FLT-1gene in a human which comprise determining the sequence of the nucleic acid of the human at position 3888 of EMBL accession number X51602, and determining the status of the human by reference to polymorphism in the FLT-1gene. Specifically, Shibuya et al. teach a method for sequencing the mRNA that encodes the FLT-1gene. The sequence of the FLT-1 mRNA determined by Shibuya et al. is the sequence provided in EMBL accession number X51062, thus encompassing the position 3888 of EMBL accession number X51602. This reference is considered to teach the

invention of claims 1 and 2 because the method contains only two method steps, one in which the sequence at position 3888 of EMBL accession number X51602 is determined (i.e. which is inherently accomplished by sequencing the portion of the gene that overlaps with position 3888 of EMBL accession number X51602), and one in which the "status of the human by reference to polymorphism" is determined. Determining the sequence of the gene is considered to inherently determine the status of the human by reference to the polymorphism because by sequencing the nucleotide present at position 3888, the status of the polymorphism is determined. The reference is considered to teach the invention of claim 19 because the sequenced gene taught by Shibuya et al. is sequenced on a computer readable medium, it overlaps with position 3888 of EMBL accession number X51602, and it is compared with other sequences to determine the identity of the FLT-1 transcript.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibuya et al. in view of Mullis (4683202).

Shibuya et al. teach a method for the diagnosis of a polymorphism in an FLT-1gene in a human which comprise determining the sequence of the nucleic acid of the human at position 3888 of EMBL accession number X51602, and determining the status of the human by reference to polymorphism in the FLT-1gene. Specifically, Shibuya et al. teach a method for sequencing

the mRNA that encodes the FLT-1gene. The sequence of the FLT-1 mRNA determined by Shibuya et al. is the sequence provided in EMBL accession number X51062, thus encompassing the position 3888 of EMBL accession number X51602. This reference is considered to teach the invention of claims 1 and 2 because the method contains only two method steps, one in which the sequence at position 3888 of EMBL accession number X51602 is determined (i.e. which is inherently accomplished by sequencing the portion of the gene that overlaps with position 3888 of EMBL accession number X51602), and one in which the "status of the human by reference to polymorphism" is determined. Determining the sequence of the gene is considered to inherently determine the status of the human by reference to the polymorphism because by sequencing the nucleotide present at position 3888, the status of the polymorphism is determined.

Shibuya et al. do not teach a method in which the nucleic acid region containing the nucleotide 3888 of EMBL accession number X51602 is amplified prior to sequencing.

However, methods for the amplification of nucleic acids by PCR prior to sequencing were routine in the art at the time the invention was made. Mullis teaches PCR, and teaches that this method is useful for producing multiple copies of a nucleic acid of interest for further genetic analysis.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have amplified copies of the FLT-1gene prior to sequencing. The ordinary practitioner would have been motivated to undertake such an amplification in order to provide more template nucleic acid for the sequencing reaction.

15. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibuya et al. in view of both Ikeda et al. (Growth Factors, 1996, Vol. 13, pp. 151-162) and Kondo et al. (GENE 208(1998) 297-305).

Shibuya et al. teach a method for the diagnosis of a polymorphism in an FLT-1 gene in a human which comprise determining the sequence of the nucleic acid of the human at position 3888 of EMBL accession number X51602, and determining the status of the human by reference to polymorphism in the FLT-1 gene. Specifically, Shibuya et al. teach a method for sequencing the mRNA that encodes the FLT-1 gene. The sequence of the FLT-1 mRNA determined by Shibuya et al. is the sequence provided in EMBL accession number X51062, thus encompassing the position 3888 of EMBL accession number X51602. This reference is considered to teach the invention of claims 1 and 2 because the method contains only two method steps, one in which the sequence at position 3888 of EMBL accession number X51602 is determined (i.e. which is inherently accomplished by sequencing the portion of the gene that overlaps with position 3888 of EMBL accession number X51602), and one in which the "status of the human by reference to polymorphism" is determined. Determining the sequence of the gene is considered to inherently determine the status of the human by reference to the polymorphism because by sequencing the nucleotide present at position 3888, the status of the polymorphism is determined.

Shibuya et al. do not teach a method wherein all of the polymorphic sites listed in claim 20 are determined, since many of those sites are within the promoter of the human flt-1 gene, or are within intronic sequences whose nucleotides would not have been determined when sequencing the mRNA.

Ikeda et al. sequenced the promoter from the human flt-1 gene, (see figure 2). This sequence includes all of the nucleotides listed in claim 20 as being in nucleotide positions 519, 786, 1422, and 1429, since each of these are within the promoter of the flt-1 gene.

Kondo et al. teach methods in which the entire genomic sequence of murine flt-1 gene in order to identify and localize the exons.

In light of all of these combined teachings, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have sequenced the entire human flt-1, including the promoter, introns, and exons. The ordinary practitioner would have been motivated to have undertaken such a sequencing effort in order to have studied the structure of the human flt-1 gene.

Conclusion

16. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Einsmann
Examiner
Art Unit 163434

January 10, 2003

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600